Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 7321

www.rsc.org/obc

PAPER

Selective reduction of ketones using water as a hydrogen source under high hydrostatic pressure

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Received 16th May 2012, Accepted 17th July 2012
DOI: 10.1039/c2ob25941a

A selective reduction of a broad variety of ketones is described. The method is based on the combination of a Ni–Al alloy and high hydrostatic pressure (HHP, 2.8 kbar) in an aqueous medium. The reaction of the Ni–Al alloy with water provides *in situ* hydrogen generation and the high pressure ensures that the H_2 formed remains in the solution, thus the C=O reduction readily occurs. The application of the HHP resulted in selective formation of the desired products and the common problem of non-selective overhydrogenation could be avoided. In most cases the reductions resulted in high yields and excellent selectivities without the use of any base.

Introduction

The reduction of carbonyl compounds is a fundamental transformation in synthetic organic chemistry.[1] New applications for these reactions are constantly being developed. The use of safe and convenient reagents and solvents is the focus of recent developments to address the ever growing concern of safety and sustainability to minimize or, preferably, eliminate waste.[2]

Activation of chemical reactions by high hydrostatic pressure (HHP) in combination with the thermal effect or catalysts provides an opportunity for the synthesis of a series of compounds.[3] The method was used for the production of hydroxy amides from lactones and amines at 9 kbar and at 30–65 °C by Otani *et al.*[4] In recent years HHP-assisted chemistry has evolved to a novel technology that fosters the development of environmentally benign processes for organic synthesis. To underline this statement several examples can be enumerated, such as sulfam production by the intramolecular Diels–Alder reaction under 13 kbar.[5] HHP-assisted chemistry was used to induce the asymmetric hetero-Diels–Alder reaction of oxindoles and isatins by Hiyoshizo *et al.*[6] The Diels–Alder cycloaddition of low reactivity alkoxybenzylideneacetone derivatives with methyl-1,3-butadienes at 8–11 kbar has been accomplished as well.[7] Transformation of lactams into ω-aminocarboxamides was also achieved in CH_3CN under 10 kbar pressure.[8] The stability and oligomerization of amino acids were investigated at 180–400 °C and 10–50 kbar.[9] Nitrogen containing heterocycles were synthesized in water using the aza-Michael reaction under high pressure conditions.[10] The hyperbaric aza-Michael reaction generated more interest, a recent paper analyses this reaction from a green chemistry point of view.[11]

Based on the literature there are several areas of chemical synthesis where HHP did and could prove to be beneficial.

One such system is when one or more of the reactants are in the gaseous phase at the temperature of the reaction, while the others are dissolved in solution. In such systems the lack of effective mass transfer from the gas to the solution could be a serious limitation. The application of high pressure increases the solubility of an otherwise hardly soluble gas in a liquid medium. Hydrogenation is probably one of the leading examples for this problem, as hydrogen is generally not well soluble in organic solvents.

Hydrogenation of aryl ketones was successfully performed over a wide range of catalysts under mild conditions leading to the corresponding alcohols.[12] For example, hydrogenation over platinum, rhodium and ruthenium was rapid and quantitative at room temperature and atmospheric pressure.[13] RANEY® nickel has also been used, giving excellent yields.[14] Supported nickel catalysts required high temperatures (100–150 °C) and high pressures (100–165 atm) and also gave almost quantitative yields.[15]

Hydrogenation of carbonyl groups occurs readily over most catalysts. However, care must be exercised in preventing side reactions of multifunctional substrates. The most common side reactions are dehydration or hydrogenolysis of the resulting hydroxyl compounds and overhydrogenation of the products to the corresponding cyclohexane and alkane derivatives.[16]

With the rise of the concept of Green Chemistry,[17] extended efforts have been made toward the use of water as a possible solvent or reagent.[18] In the field of reductions water was used as a solvent in the hydrogenation of C=N double bonds catalyzed by cyclodextrin-stabilized Pd nanoparticles.[19] Tashiro *et al.* pioneered the reduction of aryl ketones to the corresponding

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alcohols or alkane derivatives in water using various metal–Al alloys (Ni–Al, Co–Al, Cu–Al and Fe–Al).[20] While the reduction of acetophenones using a Ni–Al alloy in water under microwave irradiation proceeded to give the corresponding alkylbenzenes in good yields, the selectivity towards alcohols remained an unresolved issue due to the high reactivity of the alloy at elevated temperatures.[21]

Ni–Al alloy in a dilute alkaline aqueous solution at 90 °C has been shown to be a powerful reducing agent, which is highly effective in the reduction of phenol, naphthalenes, biphenyls, acenaphthene and benzophenones to the corresponding hydrocarbon derivatives, in the absence of any organic solvents.[22] However, the high reactivity usually results in complete hydrogenation and/or the formation of multi-component product mixtures.

Further pursuing our interest in developing new synthetic methodologies,[23] we explored the HHP-assisted chemical synthesis in hydrogenation systems where the hydrogen is generated *in situ*. Herein we describe the application of HHP in the selective reduction of ketones in water using a nickel–aluminium alloy.

Results and discussion

In order to alleviate the above-mentioned selectivity problems, we decided to apply high hydrostatic pressure to achieve more effective control over the reaction. The major advantage of the high pressure is that it would keep the *in situ* formed hydrogen in the reaction mixture. Higher hydrogen concentration in the solution would ensure that the reaction could be carried out under moderate conditions, hence resulting in improved selectivity.

First, the reduction of a broad variety of acyclic, cyclic and aryl ketones was performed with a Ni–Al alloy in water under high hydrostatic pressure. To achieve this goal we employed a Pressure Biosciences Barocycler HUB440 bench-top high pressure generator (Pressure Biosciences, Inc.), which is capable of generating and controlling hydrostatic pressure from 0.03 to 4 kbar. Depending on the sample volume up to 48 samples can be tested at the same time under identical reaction conditions in this apparatus. In the method employed, the mixture of the ketone, Ni–Al alloy and water was placed in a 150 μL MicroTube, the tube inserted into the cartridge and then the cartridge was placed in the high pressure chamber. A computer-controlled instrument maintained the reaction chamber under pressure at the desired temperature. While the instrument is capable of sophisticated dynamic pressure control over time, in this study we opted for the constant pressure option for simplicity.

In order to examine the scope and potential of this method we explored the selective reduction of various common ketones under high hydrostatic pressure in combination with heating. During the reaction, water and the aluminum content of the alloy reacted, providing the hydrogen for the reductions while the remaining Ni formed an effective high surface area RANEY®-Ni type hydrogenation catalyst.[20,21] Thus, this approach can be considered a heterogeneous catalytic hydrogenation with *in situ* generated hydrogen. The use of the high hydrostatic pressure ensured that the produced hydrogen remained in the solution, thus overcoming the common mass transfer limitations of regular hydrogenations.

Typically, 25–80 °C and 1.3–2.8 kbar was used for the selective reduction of ketones to secondary alcohols. The only remaining workup that was required is a filtration and an extraction followed by solvent evaporation.

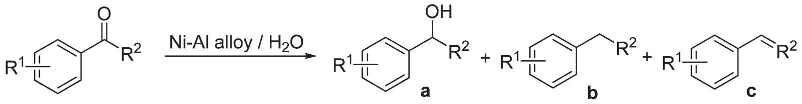
Using the above described general procedure 3-nitroacetophenone, 4-fluoroacetophenone, 4-chloroacetophenone, 3-methylacetophenone, 4-methylacetophenone, 2,4-dimethylacetophenone, 4-fluorobenzophenone and 3-nitroacetophenone were selected as model substrates to investigate the effect of experimental variables on the outcome of the reaction. For comparison, all reactions were performed at 40 °C with stirring at atmospheric pressure and under 2.8 kbar (Table 1). In addition, sonication and microwave irradiation, as alternative activation methods, were tested as well. In all cases the reaction vessel containing a mixture of a ketone (0.24 mmol, 1 equiv.), Ni–Al alloy (2.7 mmol, 11 equiv.) and water (2 mL) was stirred at a given temperature and time (Table 1). After the sample was filtered and extracted with dichloromethane, the organic layer was concentrated *in vacuo* and analyzed.

The room-temperature process is a mild reduction system; however, in several cases it gave low yield or selectivity, or no product at all (4-F-benzophenone). The other activation methods gave mixed results and no consistent picture could be drawn regarding their application. Sonication appeared to significantly activate the reduction for several starting materials (4-Cl-, 3-Me- or 3-NO_2-acetophenone) that reacted rapidly resulting in 100% conversion and 67–90% alcohol selectivities in a relatively short period of time (entries 7, 11, 27, Table 1). Other substrates, however, gave only 33–48% yield under the same conditions. The beneficial effect of ultrasounds could be at least in part explained by the well-known surface cleaning effect of ultrasonic waves.[24] Since the *in situ* generation of hydrogen is a very important part of the reaction mechanism, the clean, oxide-free aluminum surface is crucial. The removal of the surface Al_2O_3 layer shortens the induction period and results in rapid reaction rates. It, however, must be noted that the sonochemical reactions showed significant experimental errors. Depending on the placement (horizontal location and depth) of the reaction vessels in the ultrasonic bath the yields greatly varied. We found in other experiments that the sonochemical pretreatment of the RANEY alloy is useful, however, carrying out the reaction fully under ultrasonic irradiation is not recommended. Microwave-assisted reactions[25] occurred rapidly but provided poor selectivities for the alcohols compared to the other methods due to the high activity.

The application of HHP commonly resulted in controllable conditions. The reactions could be stopped at the alcohol stage since neither alkane nor alkene derivatives could be isolated as alternative products. Therefore, HPP is providing better yield and selectivity with most but not every substrate studied. It provided well reproducible conditions and consistent results. Thus it has been chosen as the activation method of choice for subsequent experiments.

For further evaluation of the characteristics of the HHP-assisted reactions, four different ketone : alloy molar ratios were tested with 3-nitroacetophenone (Fig. 1). Initially, 0.024 mmol of ketone and 0.12 mmol/0.27 mmol/0.54 mmol or 0.70 mmol

Table 1 Reduction of aryl ketones with stoichiometric amounts of a Ni–Al alloy in water under various conditions



R^1 = 4-F, 4-Cl, 3-Me, 4-Me, 2,4-diMe, 3-NO_2 R^2 = Me, Ph

						Yield[a] (%)	
Entry	Substrate	Pressure (kbar)	Energy source	Time (h)	Temperature (°C)	*C*[d] (%)	*S*[d] (%)
1	4-Fluoroacetophenone	—	—	24	40	24	96
2		2.8	—	24	40	23	100
3		—	Sonication	2	25	0	0
4		—	MW irradiation	2	80	28	0
5	4-Chloroacetophenone	—	—	16	40	82	95
6		2.8	—	16	40	25	100
7		—	Sonication	2	25	100	90[b]
8		—	MW irradiation	2	80	24	58[b]
9	3-Methylacetophenone	—	—	8	40	100	76
10		2.8	—	8	40	100	67
11		—	Sonication	2	25	100	98
12		—	MW irradiation	2	80	60	33
13	4-Methylacetophenone	—	—	8	40	100	80
14		2.8	—	8	40	100	95
15		—	Sonication	2	25	47	100
16		—	MW irradiation	2	80	100	0
17	2,4-Methylacetophenone	—	—	7	40	97	97
18		2.8	—	7	40	100	94
19		—	Sonication	2	25	48	100
20		—	MW irradiation	2	80	0	0
21	4-Fluorobenzophenone	—	—	6	40	0	0
22		2.8	—	6	40	64	80
23		—	Sonication	2	25	33	84.4
24		—	MW irradiation	2	80	52	25
25	3-Nitroacetophenone[c]	—	—	8	40	63	69
26		2.8	—	8	40	100	96
27		—	Sonication	2	25	100	84
28		—	MW irradiation	2	80	100	49

[a] GC yields. [b] Alcohol was identified as 1-phenylethanol. [c] Alcohol was identified as 1-(3-aminophenyl)ethanol in each case. [d] *C* – conversion; *S* – selectivity.

of the Ni–Al alloy in water were tested at 40 °C and 2.8 kbar. During the reaction 3-nitroacetophenone was converted to 1-(3-aminophenyl)ethanol as the main product. Although the compound contained an NO_2 group that is also known to be highly susceptible to reduction, only a small amount of 3-ethylaniline and 3-vinylaniline was determined as byproducts. The observed results, namely the yield of 1-(3-aminophenyl)ethanol, show an optimum as a function of increasing molar Ni–Al alloy/substrate ratio. At a 1 : 11 ketone : Ni–Al alloy molar ratio the complete consumption of the starting material was observed, providing the alcohol with 92% selectivity.

Initial experiments were performed to determine temperature, pressure and reaction times required to complete the transformation selectively. The first series of experiments demonstrated that reaction time depends on the structure and substituents of the ketones. The best conditions were found at 40 °C, 11 molar equivalent of alloy and a pressure of 2.8 kbar.

These results indicated that the high pressure method is a valuable selective reduction system. As a next step, we intended to map the scope of this procedure and selected a broad range of commercially available ketones, including acetophenones, benzophenones, cyclic and aliphatic ketones. The method was successfully applied for the reduction of these ketones, although the reaction conditions had to be slightly optimized according to the substrate. The results of these experiments are summarized in Table 2.

Ethyl acetoacetate, a simple β-ketoester, was chosen as a model for the reduction of an aliphatic ketone. The experiment required slightly elevated temperature (80 °C) and gave ethyl 3-hydroxybutanoate with practically quantitative yield (entry 1, Table 2). Following this encouraging result cycloalkanones were investigated to extend the variety of substrates. Similar results were observed and complete conversion of the starting material resulted in the corresponding alcohol with 100% selectivity, mostly within 6 h at 80 °C (entries 2–5, Table 2) with one example at 50 °C (entry 4, Table 2). A significant advantage of this reduction system is that it tolerates the presence of N and S atoms in the substrates. Cyclohexene derivatives containing nitrogen or sulfur atoms in the ring readily underwent reduction with high selectivity without poisoning the Ni–Al alloy or the *in situ* formed RANEY® type Ni catalyst (Table 2, entries 6–7).

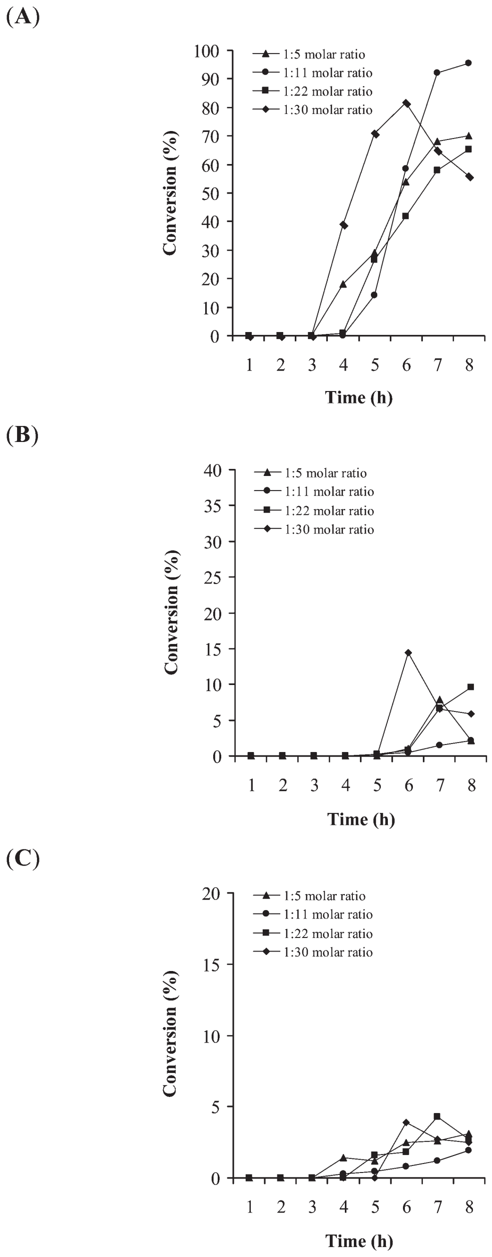
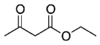
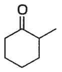
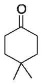
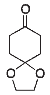
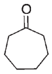
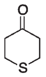
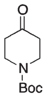
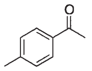
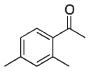
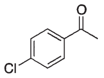
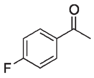
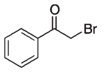
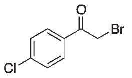
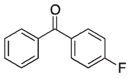
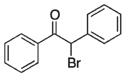
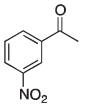


Fig. 1 Effect of the ketone : Ni–Al alloy molar ratio on the selective reduction of 3-nitroacetophenone with the Ni–Al alloy in water under high hydrostatic pressure (2.8 kbar): (A) formation of 1-(3-aminophenyl)ethanol; (B) formation of 3-ethylaniline; (C) formation of 3-vinylaniline (Note: Fig. 1B and C has different scales for better illustration).

Under the same mild conditions a variety of substituted aryl methyl ketones were hydrogenated, as shown in Table 2. Substitution of the aromatic ring with methyl groups, such as 4-methyl- and 2,4-dimethylacetophenones, led to the expected alcohols with 100% yield and 95% or 94% selectivity (entries 8–9, Table 2). Substrates bearing electron withdrawing halogen substituents at the *para* position appeared to be more challenging and provided only moderate yields (23–25%, entries 10, 11, Table 2).

Table 2 Reduction of acyclic, cyclic and aryl ketones to their corresponding secondary alcohols with a Ni–Al alloy in water under high hydrostatic pressure (2.8 kbar)

Entry	Substrate	Time (h)	Temp. (°C)	Yield[a] (%) C^d (%)	S^d (%)
1		6	80	100	100
2		16	80	100	100
3		6	80	100	100
4		8.5	50	100	100
5		6	80	100	100
6		6	80	100	100
7		6	80	100	100
8		8	40	100	95
9		7	40	100	94
10		16	50	25.5	99
11		24	40	23	100
12		16	45	92.4	54[b]
13		16	45	100	48[b]
14		16	30	64	84
15		8.5	50	45.3	98[c]
16		8	40	100	96

[a] GC yields. [b] Alcohol was identified as 1-phenylethanol. [c] Alcohol was identified as 1,2-diphenylethanol. [d] *C* – conversion; *S* – selectivity.

Next, increasing the bulkiness of the substituents, 4-fluorobenzophenone and 2-bromo-2-phenylacetophenone were reduced. They afforded the corresponding alcohols in 84% and 95% selectivity, however, the conversion decreased to 64% and 45% (entries 14, 15, Table 2), respectively. 4-Fluorobenzophenone produced the expected alcohol in good yield, while undesired further reduction to diphenylmethane (4%) or cyclohexylphenylmethane (<1%) was minimal.

Reduction of 3-nitroacetophenone was also completed. It yielded the corresponding aminoalcohol (entry 16, Table 2). In the case of nitro substituents, the first reduction step was always the transformation of nitro- to amino-group followed by the reduction of the carbonyl group.

The application of the alloy for hydrogenation of several halogenated substrates resulted in an undesired partial to full dechlorination or debromination. For example, full conversion of α-bromo-*p*-chloroacetophenone resulted in 1-phenylethanol as a major product with 48% yield (entry 13, Table 2) along with *p*-chloroacetophenone (40.6%) and vinylbenzene (less than 1%). While the carbonyl reduction was highly selective for 2-bromo-1,2-diphenylethanone (entry 15, Table 2) and no overhydrogenated products were observed the debromination resulted in the formation of 1,2-diphenylethanol.

Based on the above data, the HHP-assisted selective reduction of ketones represents a broadly applicable approach for the reduction of carbonyl compounds.

The major advantages of this approach are as follows:

(i) The reaction is highly selective for the reduction of the carbonyl group. The problems, such as overhydrogenation or multiple product formation, commonly associated with the use of the Ni–Al alloy can be largely avoided.

(ii) The reaction is carried out in water, the most benign, readily available and inexpensive solvent.

(iii) The solvent also serves as an economic source of hydrogen, thus no extra hydride or hydrogen addition is required. This is achieved without the use of any strong base.

(iv) The use of the *in situ* formed RANEY® Ni type heterogeneous catalyst allows easy product separation.

(v) The only byproduct or waste that forms during the reactions is a small amount of alumina supported Ni catalyst (Ni/Al_2O_3) that could be recycled and used as a heterogeneous hydrogenation catalyst.

Conclusions

In conclusion, a novel method for the selective reduction of various ketones has been described. The HHP-assisted transformations of acyclic, cyclic and aryl ketones to their corresponding alcohols have been conducted successfully providing a selective method for this reaction. In all of the processes the reactions were performed safely and the products were obtained in good to excellent yields and selectivities. The major advantage of this method is that the common byproducts of overhydrogenation can be completely avoided. The process, with its highly effective and selective design, provides an alternative for the selective reduction of carbonyl compounds and based on our preliminary experience it can be extended to the selective reductions of other functional groups.

Experimental

General information

All carbonyl compounds were purchased from Aldrich and were used without further purification. The Ni–Al alloy used as a reducing agent was also an Aldrich product. Solvents used in synthesis were of a minimum purity of 99.5% and were purchased from ThermoFisher Scientific. The mass spectrometric identification of the products has been carried out by an Agilent 6850 gas chromatograph-5973 mass spectrometer system (70 eV electron impact ionization) using a 30 m long DB-5 type column (J&W Scientific).

General procedure for the high hydrostatic pressure-assisted reduction of carbonyl compounds with the Ni–Al alloy in water

The reactions were carried out with a Pressure BioSciences Barocycler HUB440 bench-top high pressure generator using static pressure levels between 1.3 and 2.8 kbar in a 55 mL insulated jacketed pressure vessel. The ketone (0.024 mmol), Ni–Al alloy (0.27 mmol) and water (110 μL) were added into 150 μL fluoropolymer MicroTubes (also from Pressure BioSciences) which were placed in a stainless steel cartridge and the barocycler was set to the desired temperature and pressure. After the predetermined time the reaction was quenched by removing the cartridge from the barocycler. The samples were filtered, the filtrate extracted with CH_2Cl_2 and were directly analyzed by GC-MS. Further remaining workup was evaporation of the solvent.

Acknowledgements

The authors acknowledge financial support by the University of Massachusetts Boston; A. T. is thankful to the Rosztoczy Foundation for their financial support.

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